Chapter 6

The sequence of revascularization in liver transplantation: it does make a difference

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Introduction

No consensus exists regarding the most optimal sequence of revascularization of the liver graft during liver transplantation. The current methods of revascularization of the liver graft can be divided into two main groups (Table 1).

Table 1. Different Types of Graft Reperfusion Sequence Used in Liver Transplantation.

A	Sequential revascularization	
	A.1	With anterograde reperfusion via
		- Initial portal vein reperfusion (IPR)
		- Initial arterial reperfusion (IAR)
	A.2	With retrograde reperfusion via the IVC*
B.	Simultaneous revascularization via portal vein and hepatic artery	

**) Liver is reperfused while the portal anastomosis is being constructed. It is followed by anterograde reperfusion via the portal vein.*

The first group is sequential revascularization, in which the graft is first reperfused via either the portal vein or the hepatic artery (anterograde reperfusion), or via the inferior vena cava (IVC) (retrograde reperfusion), with subsequent reconstruction of the remaining vessels. The second group is simultaneous revascularization, in which the graft is reperfused simultaneously via the portal vein and hepatic artery. Experimental as well as clinical studies comparing different methods of revascularization are still scarce, results are not always unequivocal, and endpoints differ largely between different studies. Nevertheless, some important messages can be extracted from the current literature.

Experimental studies

Various reperfusion protocols have been analyzed in three experimental studies, using different animal models [1-3]. *Hickman and Innes.* compared two sequential protocols in pigs: initial arterial revascularization (IAR) versus initial portal revascularization (IPR) [1]. These investigators found better homogenous perfusion of the liver graft after IAR, compared to IPR. However, there were no differences in posttransplant aspartate aminotransferase (AST) serum levels among the two groups. *Van As et al.* analyzed three different sequences of graft reperfusion in a pig model: IAR, IPR, and simultaneous portal and arterial revascularization [2]. In this study, IAR was associated

with less hepatocellular reperfusion injury and better endothelial cell function, when compared to IPR or simultaneous reperfusion. No differences were found between IPR and simultaneous reperfusion, suggesting that there are no advantages of simultaneous reperfusion over IPR. Different results were obtained by *Post et al.* in a rat model of liver transplantation [3]. In their study, simultaneous arterial and portal reperfusion of the liver graft resulted in the best microcirculatory perfusion of the graft. In addition, leukocyte accumulation in the sinusoids was less and bile flow was more abundant after simultaneous reperfusion, compared to sequential reperfusion [3]. Animal studies have focused on the impact of different sequences of revascularization on hepatocellular injury and do not provide information on hemodynamic changes or injury of the biliary tree. Moreover, an important limitation of animal model is the lack of portal hypertension, which can affect the impact of IPR vs. IAR. Therefore, the best evidence should come from human observational or interventional studies.

Sequences of reperfusion in human liver transplantation

IPR vs. IAR

In the clinical setting, the most commonly used procedure for revascularization of the liver graft is initial reperfusion via the portal vein and subsequent reconstruction of the hepatic artery. This is based on the experience that portal blood flow alone is sufficient for adequate hepatocellular function [4]. Portal revascularization creates low resistant circulation with relatively low oxygen saturation. However, portal blood flow to the liver is greater than arterial flow, resulting in an overall oxygen supply to the liver via the portal vein that is at least comparable to the hepatic artery. The main disadvantage of IPR might be an increased risk of warm ischemic damage to the bile ducts, which depends solely on arterial blood supply. It is also well known that biliary epithelial cells are more susceptible to warm ischemia and reperfusion injury than hepatocytes [5]. Therefore, some authors have advocated the use of IAR [6,7]. However, a clear benefit of IAR vs. IPR with respect to the prevention of ischemic biliary injury has not been demonstrated, as is discussed below.

Simultaneous Arterial and Portal Revascularization

In simultaneous revascularization both the portal vein and arterial anastomosis are made first, followed by simultaneous reperfusion. The motivation for this protocol is the

same as for the IAR: to reduce the incidence of biliary complications [8,9]. An additional advantage of simultaneous reperfusion is that, in case of a problem with one of the two anastomoses, this can be repaired without completely interrupting blood flow to the graft. The disadvantage of simultaneous revascularization is prolongation of the warm ischemia time and the anhepatic phase, which can be detrimental to postoperative graft function, survival and morbidity [10,11].

Retrograde reperfusion via the IVC

In recent clinical studies, a new technique has been advocated with retrograde reperfusion via the IVC followed by subsequent anterograde reperfusion via the portal vein [12,13]. In this technique the vascular clamp on the IVC is removed immediately after completing the IVC anastomosis, allowing retrograde reperfusion while the portal vein anastomosis is being constructed. The rationale behind retrograde reperfusion via the IVC is that it shortens the WIT and efficiently removes perfusion fluid from the graft before anterograde blood flow is reestablished. Hypothetically, low pressure perfusion with low oxygenated venous blood could also reduce the production of free oxygen radicals, and thus might reduce postreperfusion injury [12].

The available studies comparing different revascularization protocols can be divided into two groups according to the outcome parameters. The first type of studies focuses on the impact of reperfusion sequence on postoperative graft function and biliary complications, such as ischemic-type biliary lesions (ITBL). The second type of studies focuses on changes in systemic and pulmonary hemodynamcis as well as tissue metabolism.

Influence of reperfusion sequence on graft function and biliary strictures

In a randomized clinical study, *Millis et al.* compared four different reperfusion techniques: IPR with or without IVC venting, and IAR with or without IVC venting [4]. These investigators found no differences in postoperative graft function between the four groups. However, the lowest incidence of postreperfusion syndrome was observed in the group of IPR without IVC venting, whereas IVC venting decreased the release of potassium into the circulation. In a controlled study comparing IAR with IPR, *Noun et al.* demonstrated that IAR provides better graft reperfusion, lower requirements of

blood transfusion and antifibrinolytic medication, as well as a shorter postreperfusion phase in comparison to IPR [6]. However, there were no differences in postoperative AST serum levels, factor V plasma levels, bile flow and early postoperative vascular and biliary complications between the two revascularization methods. Similar results regarding postoperative graft function (as assessed by lactate concentrations, alanine aminotransferase (ALT) serum level and prothrombin time) after either IPR or IAR were reported by *Sadler et al.*, despite the fact that the WIT was significantly longer in grafts with IAR [14]. Moreover, there were no differences in the intraoperative use of blood products and in 30-day and 1-year mortality between IPR and IAR in this study [14].

Three relevant studies are available comparing sequential reperfusion via portal vein with simultaneous arterial and portal reperfusion. In a retrospective study, *Sankary et al.* compared sequential reperfusion (portal vein first) with simultaneous portal and arterial reperfusion [8]. In the latter group significantly less non-anastomotic biliary strictures were observed compared to the sequentially reperfused grafts. *Massarollo et al.* also compared the two reperfusion protocols in a retrospective study [9]. They also found no differences in patient and graft survival rates or the incidence of primary non-function. Biliary complications, however, were also less frequent in the simultaneous reperfused group, compared to the sequentially reperfused group [9]. Interestingly, however, the biliary complications in this study concerned mostly anastomotic strictures (6/9) and only one non-anastomotic stricture was observed. In contrast to these two studies, we recently reported no significant differences in patient and graft survival, morbidity rates, incidence and severity of acute rejection, recuperation of liver function, or the incidence of ITBL, when comparing sequential versus simultaneous reperfusion [15]. However, in our study the cold ischemia time (CIT) was substantially shorter (median 8.7 hours) than in the two earlier studies (median CIT of 10.7 hours and 13.3 hours, respectively). Our results, therefore, suggest that the order of revascularization does not influence the incidence of ITBL when the CIT is kept relatively short (< 9 hours).

Three studies analyzed retrograde reperfusion with respect to the postoperative function and postoperative complications [12,13,16]. In two retrospective series, *Kniepeiss at al.* showed that retrograde reperfusion via the IVC with subsequent anterograde reperfusion via the portal vein results in favorable values of postoperative serum liver enzymes, bilirubin, prothrombin time, antithrombin III and low incidence of postreperfusion syndrome [12,13]. In a more recent study, the group from Berlin compared retrograde revascularization with simultaneous revascularization in a prospective, randomized clinical trial [16]. In a preliminary report, these investigators reported significantly reduced

serum transaminases and bilirubin levels in the first posttransplant week as well as lower incidence of primary non-function and initial poor function in the retrograde reperfused grafts, compared to simultaneously reperfused grafts. However, ischemic-type biliary lesions (ITBL) occurred more frequently in livers with retrograde revascularization via the IVC [16].

Influence of reperfusion sequence on hemodynamics and metabolism

Oxygen consumption after either IPR or IAR has been studied by *Walsh et al.* [17]. These investigators found a slower increase in oxygen consumption after reperfusion in patients with IAR compared to patients with IPR. In a prospective randomized study, *Ducerf et al.* showed more stable hemodynamics (assessed by mean arterial pressure, central venous pressure, cardiac index, systemic vascular resistance and pulmonary capillary pressure) and lower peak values of serum AST after IAR, compared to IPR [7]. Similar to previous animal studies, they also observed a more homogenous graft reperfusion in the IAR group [1]. No differences were found between the IAR and IPR group with respect to the intraoperative blood products transfusion requirements or the use of antifibrinolytic drugs. In a prospective, nonrandomized study, *Walsh et al.* reported no differences in either cardiovascular parameters or postoperative serum ALT levels between IAR grafts and IPR grafts, although epinephrine requirements were lower in the IAR group [18]. The IAR group showed lower increase in $PaCO_2$ and a trend towards less severe academia, as well as a slower increase in VO_2.

In this issue of Liver Transplantation, *Moreno et al.* report a prospective, randomized study comparing hemodynamic profile and tissue oxygenation during reperfusion of the graft via either IPR or IAR [19]. These investigators randomly included 30 patients in each revascularization protocol. After completing both the portal and arterial anastomoses, the hepatic artery was opened first in the IAR group, followed by portal vein unclamping after 10 minutes. A reversed order of unclamping of the portal vein and hepatic artery was used in the IPR group, again with 10 min delay between the two vessels. The investigators found a higher mean pulmonary wedge pressure and central venous pressure, as well as higher pulmonary vascular resistance after unclamping in the IPR group, compared to the IAR group. There were no significant differences in the levels of postoperative serum transaminases between the two groups. Arterial pH decreased

in both groups and recovered by the end of procedure; however, arterial pH, lactate and venous oxygen saturation were better for the IPR group. In accordance with the previous study by *Walsh et al.*, oxygen consumption and oxygen delivery were higher in the IPR group, especially after the second vessel was opened [17].

Based on these data, the following can be concluded: IPR offers more favorable perfusion and metabolic behavior than IAR. However, IPR causes an acute increase in pulmonary vascular load, which may become critical in patients with poor cardiopulmonary reserve (i.e. with pulmonary hypertension or cardiomyopathy). Overloading of the pulmonary circulation is avoided in IAR, resulting in a less markedly increase of the pulmonary artery pressure. IAR, therefore, may be indicated in patients with a poor pulmonary and cardiac reserve [19,20]. Although the study by *Moreno et al.* provides important new information on the metabolic and hemodynamic consequences of IAR and IPR, the results are not a complete surprise, when considering normal blood flow physiology of the liver. About 70 to 80% of the blood flow through the liver comes from the portal venous circulation and the remaining is provided by the hepatic artery. Therefore, initial reperfusion via the portal vein may provide good blood flow to the liver parenchyma, but is also causes a more rapid increase in venous return from the hepatic veins to the right atrium and pulmonary circulation. Initial unclamping of the hepatic artery, on the other hand, causes relatively low blood flow through the liver and subsequently a low increase of volume load to the right atrium and pulmonary circulation. The slower increase in oxygen consumption suggests that IAR, paradoxically, also provides less efficient initial oxygen delivery to the liver graft than IPR.

Summary and conclusions

Knowledge about the most optimal sequence of revascularization of liver grafts is gradually emerging (Table 2). Sequential revascularization allows a short WIT, which has been shown to be a clinically important determinant of outcome and initial hepatocellular function.

With regard to postreperfusion liver injury there are no significant differences between IAR and IPR. Also the more recently advocated method of retrograde reperfusion via the IVC seems to provide good postoperative liver function with a low incidence of initial graft dysfunction. However, data suggest that this method, similarly to IPR, carries a higher risk of ITBL, probably because of lack of arterial flow to the bile ducts in

the progressively rewarming graft, causing ischemic injury to the biliary epithelium. Although the aim of simultaneous arterial and portal reperfusion has been to prevent biliary complications, the available results are conflicting and not conclusive. Moreover, the prolongation of WIT and anhepatic phase associated with simultaneous reperfusion may have an overall negative impact on postoperative graft function.

Table 2. Potential Advantages and Disadvantages of Various Sequences of Reperfusion in Liver Transplantation.

	Advantages	Disadvantages
Anterograde reperfusion		
- Initial portal reperfusion (IPR)	- Short warm ischemia time - Establishes good blood flow to parenchyma	- Acute increase in pulmonary vascular load (increases CVP and PAP) - Prolonged warm ischemia to bile ducts
- Initial arterial reperfusion (IAR)	- Immediate restoration blood flow to bile ducts - Avoids acute overload of the pulmonary circulation	- Less overall blood flow to graft than with IPR
- Simultaneous reperfusion	- Simultaneous restoration of blood flow to liver parenchyma and bile ducts	- Significantly prolonged warm ischemia time
- Retrograde reperfusion via IVC	- Very short warm ischemia time - Hemodynamic stability	- Prolonged warm ischemia to bile ducts, more ITBL

Abbreviations used: CVP, central venous pressure; ITBL, ischemic-type biliary lesions; IVC, inferior vena cava; PAP, pulmonary artery pressure; WIT, warm ischemia time.

With respect to the hemodynamic changes associated with graft reperfusion, IPR seems to offer a more favorable immediate perfusion, compared to IAR. However, IAR is associated with less increase in pulmonary artery pressure and may, therefore, be indicated in patients with a poor cardiopulmonary reserve. Apart from these general differences, the anatomical situation in an individual patient can make one technique preferable over the other. For example, in case of extensive portal vein thrombosis, it is sometimes safer to construct the arterial anastomosis first, securing blood flow to the liver and avoiding extra warm ischemia when thrombectomy of the portal vein (unexpectedly) has not resulted in optimal restoration of hepatic blood flow. Another aspect is that the portal vein anastomosis is usually technically easier and more straightforward than the arterial anastomosis. The latter is more prone for technical failure and sometimes requires more time and concentration.

To provide better insight in the consequences of various reperfusion protocols, more randomized clinical studies, such as performed by *Moreno et al.*, will be needed [19].

Such studies would require several hundreds of patients in each study arm to have enough statistical power and to make any firm conclusions [14]. This implies the need for multicenter collaboration. The sequence of graft reperfusion may be particularly relevant in compromised liver grafts, such as livers from non-heart-beating donors, older or steatotic donors, as well as small-for-size grafts in living donor liver transplantation. This subject has not received much attention so far and more research in this area is warranted.

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